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CHOLANGIOCARCINOMA - PRESENTATION OF A RAPIDLY PROGRESSIVE CASE

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ABSTRACT

This is a case report with a rapidly progressive presentation and late diagnosis of cholangiocarcinoma compatible with poorly differentiated carcinoma, favoring the biliary/pancreatobiliary origin. There are several hypotheses for the etiology that remains ill-defined. We made a brief correction of the biomarkers and immunohistochemistry of the case with the literature. The articles selected for literary review were taken from the pubmed platform, scielo and google academico. Data collection and field research were carried out with the aim of maintaining confidentiality and respect for patients and third parties.

INTRODUCTION

Cholangiocarcinoma is a malignant tumor originating from the epithelium of intrahepatic or extrahepatic bile ducts. First described by Durand-Fardel in 1840. (Burgos L, 2008). Malignant liver tumors and cholangiocarcinoma account for about 95% of primary liver cancers. However, there are several other little-known and underdiagnosed tumors. (Araneda, 2019).

METHODOLOGY

It is a descriptive, narrative and reflective study, through a case report entitled: "Cholangiocarcinoma: presentation of a rapidly progressive case"; data collection and field research were carried out with the aim of maintaining confidentiality and respect for patients and third parties. The patient is followed up by the routine of the ward and the intensive care unit, during the hospital stay, where the electronic medical record and data necessary for the study, such as photographic records (eg, images such as cranial tomography, total abdominal ultrasonography and cholangioresonance biliary). Location of the research field: Hospital Casa de Saúde Santa Maria Barra Mansa – RJ. This study consists of a case report research project of a female patient, 76 years old, brown, retired, born and resident of Barra Mansa; and aims to demonstrate the need to identify biomarkers to assist in the effective diagnosis of cholangiocarcinoma during the initial phase of the disease, advancing with new tests that allow early diagnosis, improving its prognosis.

The current classification according to the World Health Organization (WHO) and the Union for International Cancer Control (UICC) includes only two categories, according to the anatomical origin along the biliary tract:
- Intrahepatic cholangiocarcinoma (ICC), develops within the liver, from the secondary bile ducts and the proximal intrahepatic bile ducts;
- Extrahepatic bile duct carcinoma (eBDC), includes tumors arising from large hepatic hilar bile ducts (also called Klatskin tumor) and distal extrahepatic bile ducts (Hoyos et al, 2019)

Diagnosis is usually late based on clinical symptoms, laboratory tests, endoscopy, and imaging tests. The difficulty in resection of these tumors is fundamentally caused by three reasons: late diagnosis, neoplastic infiltration of the vasculature of the hepatic hilum and lack of specialists sufficiently trained in the hepatobiliary surgery necessary for these cases, whose procedure is highly complex (Del Valle et al, 2021).

Some treatments have been proposed to improve survival and despite the poor prognosis, imaging diagnosis has advanced and brought hope for a more favorable outcome.

Presentation of the case

Patient M.M.P., female, 76 years old, brown, retired profession, born and resident of Barra Mansa. She has systemic arterial hypertension, diabetes mellitus, hypothyroidism, obesity and depression. Continuous use of valsartan, atenolol, metformin, glibenclamide, levothyroxine, desvenlafaxine and lurasidone. Report of using paracetamol sporadically. She came to the consultation complaining of anorexia, asthenia, drowsiness and significant weight loss of 25 kg in the last year. There was no significant jaundice in the initial phase, but abdominal pain prevailed. She denies changes in bowel habits, bleeding, pruritus or arthralgias. He denies alcoholism or smoking. She was referred by the psychiatric service due to changes in liver laboratory tests.

On physical examination

Patient in regular general condition, oriented in time and space. Stained and hydrated mucous membranes, jaundice +/4+, afebrile. eupneic. BMI: 37

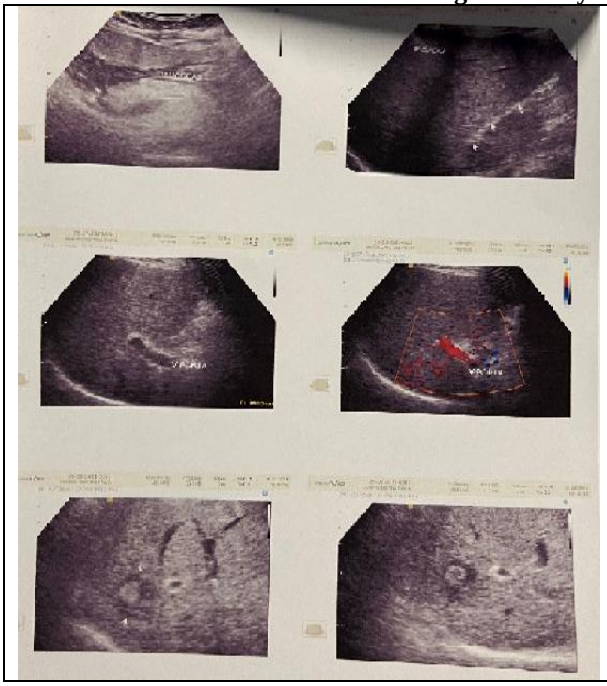
Cardiovascular examination without changes. Respiratory system examination: Universally audible breath sounds, diminished in bases. Flaccid, globose abdomen, peristalsis present, diffusely painful, worse in the right hypochondrium. Lower limbs without edema, palpable pulses and free calves.

During the consultation, he brought previous exams. Table 1.

Table 1: Laboratory tests at the initial consultation.

	Janeiro 2019	**Janeiro 2021**
Glicose	342	156
Hemoglobina glicada	12,1	10,5
Uréia	26	38
Creatinina	1.1	0.9
TSH	2,35	1,82
Aspartato aminotransferase	74	62
Alanina aminotransferase	103	58
Fosfatase Alcalina	58	73
Gama glutamil transferase	141	413
Bilirrubina Total	0.7	0.5
Bilirrubina Direta	0.3	0.3
Bilirrubina Indireta	0.4	0.2
Ferritina serica	111,75	33,36
Colesterol total	235	206

PHOTO 1: Total abdomen ultrasound showing secondary liver implants, report attached:



Total abdomen ultrasound report

The liver has a normal volume, a somewhat irregular surface, thin borders and a homogeneous internal texture with diffuse micronodularity, suggestive of chronic liver disease. Presence of an irregular hyperechoic nodule, with a peripheral hypoechoic halo, not circumscribed, measuring 29 x 22 mm located inside the right hepatic lobe (segment VIII). Portal branches and suprahepatic veins have conserved calibers. Gallbladder not evident. Intra and extra hepatic bile ducts without evidence of dilatation. A solid, hypoechoic, lobulated, heterogeneous nodular lesion measuring 28 x 18 mm was observed in the topography of the left adrenal. Rest of the exam unchanged.

During the consultation, the investigation was started for diseases that promote cholestasis, with the main hypothesis being obstructive lesions of the bile ducts, autoimmune diseases and hepatitis caused by drugs. New laboratory tests were requested, including serology for viral hepatitis, ANA, anti-smooth muscle, protein electrophoresis, ferritin, transferrin saturation, iron, anti-mitochondrial antibody, p-ANCA and other markers. Nuclear magnetic resonance cholangiography was

also requested to investigate cholestasis and total abdominal resonance to evaluate hepatic and adrenal nodules.

Only laboratory tests were performed where the high serum GGT dosage is noteworthy. The exams are shown in Table 2.

Table 2. Laboratory tests at the outpatient clinic.

	Janeiro 2022
Hematócrito	45.0
Hemoglobina	14.2
Leucócitos	8.122
bastões	1%
plaquetas	155.000
Glicose	76
Hemoglobina glicada	5,6
Uréia	36
Creatinina	0.8
TSH	0.063
Aspartato aminotransferase	30
Alanina aminotransferase	140
Fosfatase Alcalina	**165**
Gama glutamil transferase	**505**
Bilirrubina Total	1.1
Bilirrubina Direta	0,5
Bilirrubina Indireta	0.6
Amilase	93
Lipase	62
Ferritina serica	403,04
Colesterol total	219
FAN	Nao reagente

Before performing the imaging tests, the patient evolved with a fall from his own height and needed to be hospitalized. During hospitalization, a cranial tomography was performed, which showed subarachnoid hemorrhage in the left parietal region and subcutaneous hematoma in the right parietal region. Evaluated by neurosurgery that considered conservative treatment. He was discharged from the hospital to continue the liver investigation on an outpatient basis.

After 05 days with clinical worsening, unable to perform the outpatient exams, maintaining asthenia and inappetence and jaundice, he returned for hospitalization with the aim of diagnostic elucidation. Nuclear magnetic resonance cholangiography was performed. In the follow-up, a progressive and expressive increase in GGT, FA and total bilirubin and fractions was observed, as well as other markers, as shown in Table 3 below:

Table 3. Laboratory tests during hospitalization.

	01/02/2022	**16/02/2022**	**22/02/2022**
hematocrit	41.0	42.3	41.3
Hemoglobin	13.8	14.5	14.0
leukocytes	5.100	5.200	6.500
sticks	0%	0%	0%
platelets	102.000	93.000	87.000
Urea	39	45	46
creatinine	0.73	0.82	0.89
Aspartate aminotransferase	224	435	493
alanine aminotransferase	66	70	109
Alkaline phosphatase	**259**	**617**	**544**
Gamma glutamyl transferase	**758**	**1329**	**1411**
Total Bilirubin	**1.76**	**2.18**	**8.92**
Direct Bilirubin	**0.99**	**1.43**	**7.49**
Indirect Bilirubin	0.77	0,75	1.43
INR	1.27	1.05	1.09
TAP	13,0%	12.5%	13%
ferritin	580	-	-
LDH (reference up to 246)	-	930	1070
Albumin	3.9	3.04	2,8
CA-125	-	**60,2**	**64,9**
CA19-9 (reference up to 37)	-	**1590**	**1693**
CEA (reference up to 3.0)	-	4.3	-
IgM immunoglobulin (reference up to 300)	-	331	-

IgG immunoglobulin (reference up to 1600)	-	1.714	-
IgA immunoglobulin (reference up to 350)	-	601	-
Alpha Fetoprotein (reference up to 8.1)	-	20.2	19.9
Beta-2-Microglobulin (reference to 2164)	-	5220,0	-
IgG toxoplasmosis	reagente	-	-
cytomegalovirus IgG	reagente	-	-
Epstein Barr IgG	Reagente	-	-
Anti HBC IgG	Nao reagente	-	-
Hepatitis B – HbsAg	Nao reagente	Nao reagente	-
Hepatitis B – ANTI HBs	Nao reagente	Nao reagente	-
Hepatitis B – ANTI HBC IgM	Nao reagente	Nao reagente	-
Hepatitis B – ANTI HBC IgG	Nao reagente	Nao reagente	-
Hepatitis C – ANTI HCV	0,11	0.04	-
FAN	Nao reagente	Nao reagente	-
alpha 1 antitrypsin	197	-	-
Anti neutrophil cytoplasm	Nao reagente	-	-
anti smooth muscle	Nao reagente	-	-
anti mitochondria	Nao reagente		
serum ferritin	580	-	-
Ceruloplasmin	33	-	-
Seric iron	73	-	-
Total iron binding capacity	211	-	-
transferrin saturation index	34,6	-	-

Nuclear magnetic resonance cholangiography report (02/16/2022)

Sparse expansive/nodular lesions in the liver parenchyma, notably the right lobe, compatible with neoplastic lesions, and the possibility of cholangiocarcinoma and secondary implants should be initially considered. Multiple lymph node enlargement/retroperitoneal lymph node conglomerates, next to the hepatic hilum and adjacent to the pancreatic head, with a compromised appearance. Presence of ascites.

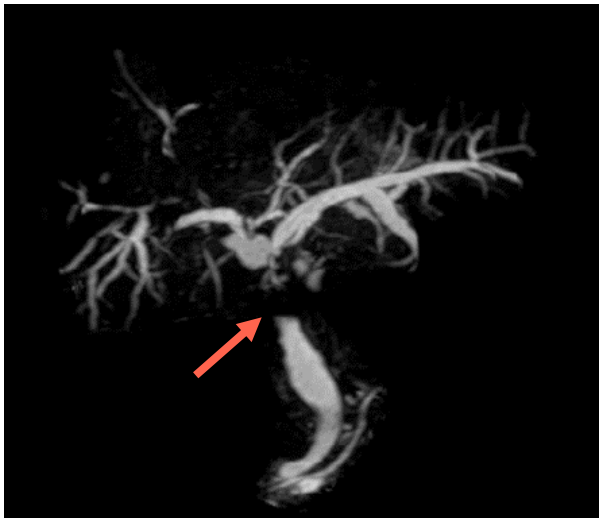


PHOTO 2: 3D reconstruction showing filling failure locating the lesion with intra and extra hepatic bile duct dilatation.

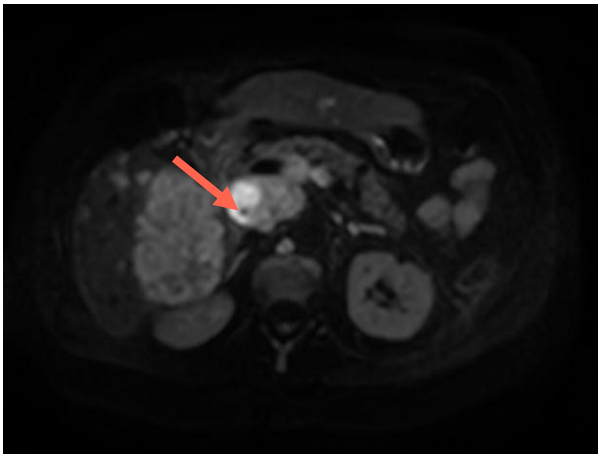


PHOTO 3: diffusion sequence pointing to the cholangiocarcinoma mass, showing the exact location of the tumor that obstructs and loses the hepatocholedochus causing dilatation of the bile ducts.

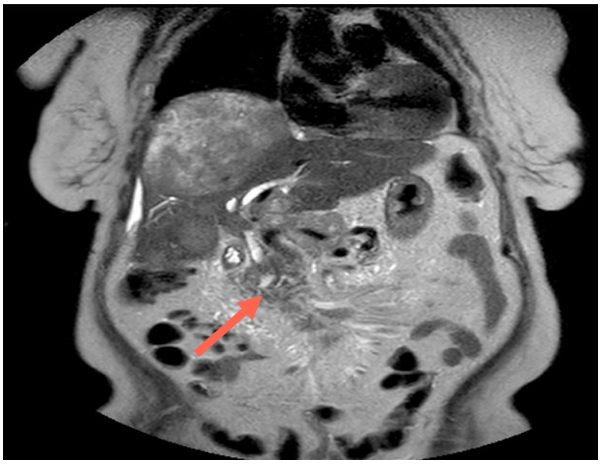


PHOTO 4: T2 coronal section pointing to the lesion and abrupt loss of definition of the hepatocholedochus returning to visualization with dilatation of the intra hepatic bile ducts. It also shows the most anterior and superior segment of the liver visualizing liver metastasis.

After the physical examination and evaluation of the results of the complementary exams received, the case was discussed together with the family, the assistant physician of the Internal Medicine and the Gastroenterologist. It was then decided to perform a liver biopsy by tomography, whose report showed carcinoma with trabecular and chordal arrangement infiltrating hepatic parenchyma, in addition to the presence of necrosis and desmoplastic reaction. Such material was sent for immunohistochemical study with the following results. Table 4.

Table 4. Immunohistochemistry Result.

POSITIVES
EMA (epithelial membrane antigen), CD 10 (canalicular pattern), CD 34 (sinusoidal pattern), Ck 19, Ki 67 (95% positive), p63 and Cam 5.2.
NEGATIVES
CD56, CEA, cytokeratins 5/6/7/20, chromogranin, HepPar-1, HMB45, S100 protein, estrogen and progesterone receptor, synaptophysin, WT-1, GATA-3, glypican-3.
RESULT
profile associated with morphological findings is compatible with carcinoma (poorly differentiated) favoring biliary/pancreatobiliary origin.

After the definitive diagnosis of cholangiocarcinoma, with probable Klatski's Tmor, there was a significant clinical worsening of the patient's physical status. She evolved with renal failure and metabolic acidosis in the coming weeks, was referred to the intensive care service under palliative care, and her death was recorded on 03/12/2022.

DISCUSSION

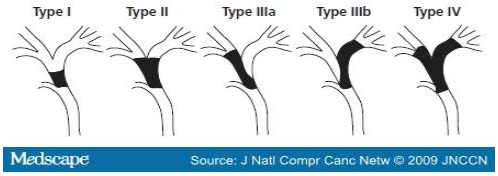
Primary liver cancer is the second most important cause of global cancer mortality. Hepatocellular carcinoma is the most prevalent type of primary liver cancer in most countries, accounting for about 80% of cases. The second most common primary liver cancer is cholangiocarcinoma (CCA), accounting for approximately 15% of cases and < 3% of all malignant gastrointestinal tumors, with wide geographic variation, reflecting exposure to different risk factors (Hoyos et al., 2019).
The incidence of cholangiocarcinoma appears to be increasing and may be as high as 2.1 per 100,000 person-years in Western countries. (Bridgewater J, 2014). It is the second most common primary liver malignancy and its incidence still has unknown reasons. We also cannot exclude that more diagnoses are being made due to new and better diagnostic methods available for obstructive jaundice, which can identify biliary malignancies that may not have been diagnosed previously. (Coelho, 2017).

It can be located at any level of the bile duct. Depending on its anatomical location, it is classified into three subtypes: intrahepatic (15-20%), perihilar (60-70%) and distal (20-30%). Most cholangiocarcinomas are of the ductal adenocarcinoma type, but they can also be papillary, mucinous, mucoepidermoid and cystadenocarcinoma adenocarcinomas (Del Valle et al, 2021).

Cholangiocarcinoma can appear anywhere in the biliary tree (from the intrahepatic canaliculi to the ampulla of Vater), with the perihilar section (area where the main hepatic ducts converge) being the most frequently affected, representing between 40 and 60% of the total. ; this subtype is called Klatskin

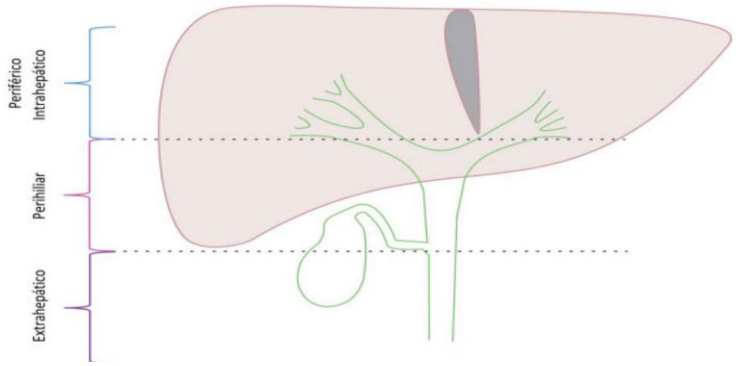
tumor (hilar cholangiocarcinoma). (Méndez H.F, 2014)

Klatskin tumor is the most common malignant tumor that affects the extrahepatic bile duct. It is relatively slow growing and small on clinical examination. Your treatment is challenging. (Xiang, 2015)



Source: https://www.gastrobenw.be/classificaties-scores

Figure 1: Klatskin tumor classification according to the Bismuth-Carlette system.



Source:. (Sánchez L. et.al, 2019)

Figure 2: Classification by anatomical location of cholangiocarcinoma.

The clinic is usually nonspecific. Among the main complaints we highlight anorexia, weight loss and general malaise. The most important sign is progressive jaundice, present in about 90%. It is a silent disease, with a difficult diagnosis to be performed early. The lack of specific markers also makes it difficult to identify the disease, delaying its diagnosis. (Castro Sousa et al, 2012).

In the clinical picture, in general, weight loss, progressive jaundice and pain in the right hypochondrium stand out, and the differential diagnosis of periampullary lesions is important. (Burgos L, 2008). In the case studied, weight loss and progressive jaundice prevailed in the last three weeks, in addition to intense fatigue and lack of appetite.

Intrahepatic cholangiocarcinoma presumably arises from small ducts within the liver, growing insidiously to large volumes before the patient becomes symptomatic. In contrast, ductal cholangiocarcinoma arises from large ducts, up to the second branching order, and patients present earlier biliary tract obstruction (Hoyos et al, 2019)

These tumors are characterized by slow growth, but usually with a pattern of local infiltration. Carcinogenesis is characterized by the presence of desmoplastic stroma, fibrogenic process, immune response and angiogenesis. There was an increase in incidence rates, especially in the group of patients ≥ 65 years. (Hoyos et al, 2019).

The etiology of cholangiocarcinoma is not defined. However, some pathological processes would be predisposing. These include primary sclerosing cholangitis, intrahepatic lithiasis, Caroli's disease, and malformations such as biliary atresia and bile duct cysts. There is also association with carcinogenic toxic substances of industrial origin, such as digoxin, nitrosamines and asbestos. In addition, it is associated with chronic bile duct infestation with parasites endemic to Southeast Asia, such as Clonorchis sinensis and Opisthorchis viverrin. Chronic salmonella typhi infection would be another predisposing factor. (Burgos L, 2008). Hoyos et al, 2019 also relates this worm with liver infection inducing chronic inflammation mainly in the small intrahepatic ducts and gallbladder. C. Sinensis is identified as a human carcinogen while O. viverrini is likely considered a human carcinogen according to the International Agency for Research on Cancer (IARC).

Chronic inflammation has been attributed to initiating, aiding, or inducing tumor growth in various diseases that, in turn, can result in cancer. Aberrant production of interleukin (IL)-6, a proinflammatory cytokine, has been correlated with the predisposition of chronic inflammation of the biliary tract to cholangiocarcinoma. (Bhakta et.al., 2015)

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are likely to be associated with hepatocellular carcinoma; however, these viral infections are also being considered as an important risk factor for cholangiocarcinoma development. (Bhakta et.al., 2015).

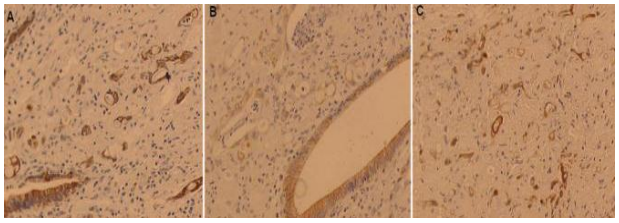
Tumor markers CA 19-9, CA-125 and CEA are increased in cholangiocarcinoma but are not pathognomonic for these lesions. They also appear in other malignant pathologies and in severe liver damage. (Del Valle et al, 2021).

There is no specific marker that makes early diagnosis possible. Generally, the worsening of liver function is related to the greater severity of the disease, as seen in this case. Some researchers consider that CEA, but not CA19.9, is associated with a poor prognosis. (Uenishi T, 2001) This data remains controversial, as reported by Ohtsuka and Huang, who in their analysis considered CA19.9 the main marker of severity. (Castro Sousa et al, 2012). L Burgos also presents a comparative study between CA 19-9 and CEA performed by Chinese authors who showed that CA 19-9 is more useful for the diagnosis of cholangiocarcinoma. In our case report, the patient presented a significant increase in CA19-9.

Immunohistochemistry is the best way to determine the origin of the tumor, but to date, there are no specific markers. Intracellular carcinoma tumor cells are positive for the biliary subtype of cytokeratins ck7 and ck19. However, some metastatic adenocarcinomas may present an immunohistochemical profile similar to intracellular carcinoma characterized by positive staining of CK7 and CK19. (Hoyos et al, 2019). In the case reported, the immunohistochemical result was positive for Ck 19 and negative for CEA.

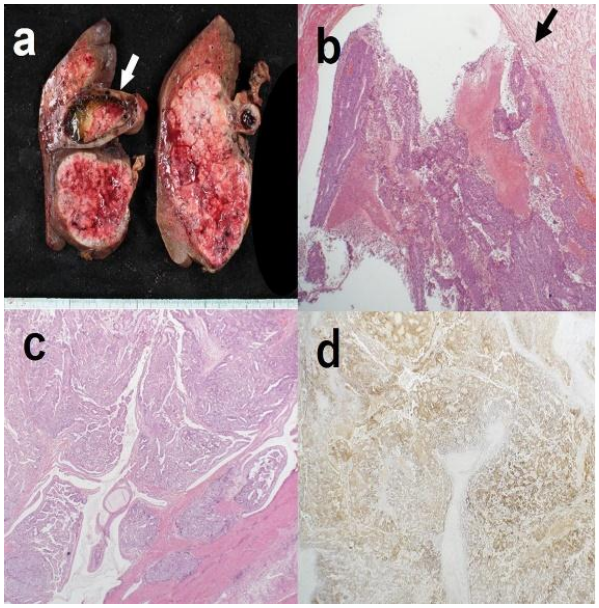
The recent development of biochemical methodologies has contributed to the clarification of the histogenesis of several malignant neoplasms, including not only hematopoietic tumors, but also solid tumors, and the cancer stem cell theory has paved the way for understanding the histogenesis of several of these neoplasms. The last edited WHO classification published in 2010 adopted the stem cell/HPC concept in the pathological classification of HCC. (AKIBA et al, 2019).

The case pathology report revealed a positive result for: EMA (epithelial membrane antigen), CD 10 (canalicular pattern), CD 34 (sinusoidal pattern), Ck 19, Ki 67 (95% positive), p63 and Cam 5.2. In the work by Chedid et.al. he attaches a slide with the signet cells stained for CK 19 and CAM 5.2, with the same positive result as in the case described above.



Source: Figure taken from CHEDID M.F. et al, 2015
Figure: Signet ring cells stained for (A) CK19 (x 200); (B) CK07, (x 200); (C) CAM5.2, (x 200).

According to Akiba et.al, immunohistochemical markers show characteristics of stem cells/HPC (liver progenitor cells) that are also non-specific. Several markers are recognized as stem cell/HPC markers, and some of them are used as markers of biliary differentiation, such as CD56, K19 and EpCAM. In the case cited, the report shows positive for CAM 5.2 and negative for CD 56, and results compatible with carcinoma (poorly differentiated) favoring biliary/pancreatobiliary origin.



Source: Figure taken from Hanazawa, 2021.
Figure 2: The Cut surface of the resected pieces shows fused multinodular lesions in the liver and papillary tumor in the gallbladder with arrow.
b Liver sample shows a component of poorly differentiated HCC cells with trabecular and solid growth and diffuse invasion of the portal vein including with arrow (×20, H&E stain).
c Tumor cells in the gallbladder show a trabecular pattern indicating HCC (×40, H&E stain).
d Gallbladder tumor immunostaining is positive for AFP (×20, H&E stain)

The case reported showed carcinoma with trabecular and chordal arrangement in the biopsy, infiltrating hepatic parenchyma, and in the immunohistochemical test, poorly differentiated carcinoma. Figure 2b shows poorly differentiated cells with trabecular and solid growth; figure 2c

shows trabecular pattern indicating HCC. Figure taken from Hanazawa, 2021.
To elucidate the diagnosis, imaging tests begin with ultrasound, which is especially important in cases of investigation of cholestatic syndromes. Color Doppler ultrasound allows visualization of portal involvement. Resonance cholangiography has the advantage of being a non-invasive exam that visualizes both the hepatic parenchyma and the bile duct, in this case it was essential to elucidate the diagnosis. (Del Valle et al, 2021).

In addition to nuclear magnetic resonance cholangiography, there are important endoscopic exams for the diagnosis of these lesions. Among them, we highlight endoscopic retrograde cholangiopancreatography (ERCP), which allows endoluminal brushing and obtaining samples for cytological study. In addition, ERCP also has a therapeutic role, with the possibility of palliatively placing biliary prostheses to promote drainage and clinical improvement in patients. Another important test is endoscopic ultrasonography, which can be used to visualize the tumor mass and promote the acquisition of puncture and aspiration biopsies. (AKIBA et al, 2019). In the case in question, the histopathological diagnosis was made by interventional radiology due to the availability of this method in the hospital and the experience of the performing professional.

The combination of a usually late diagnosis with the absence of alternatives to surgical treatment makes this tumor usually considered a tumor with a poor prognosis. (Castro Sousa et al, 2012).

The ideal treatment for cholangiocarcinoma is surgical resection, unfortunately, in most cases the tumor is unresectable. For these cases, there is the possibility of palliation through the placement of stents.

endoscopic or percutaneous. (Del Valle et al, 2021). In this case, the tumor was discovered late, associated with clinical instability, and it was not possible to perform the endoscopic procedure.

The palliative treatment of choice in Klatskin's tumor is the resolution of jaundice and pruritus by endoscopic biliary drainage as a first option, or percutaneously as an alternative in case of complications of the endoscopic method. Radiotherapy, chemotherapy and liver transplantation have not shown significant utility in improving the life expectancy and quality of life of patients affected by this neoplasm. (Méndez H.F, 2014).

Recently, in Dutch and Swiss centers, they used endoscopic phototherapy associated with endoscopic drainage, as a locoregional palliative therapy that provides better survival than single biliary drainage. It consists of the intravenous administration of a photosensitizer and then the endoscopic application of a beam of light of a certain length, a wave with which a tumoricidal effect of 4 mm in depth is achieved. (AKIBA et al, 2019)
The recent FDA approval of pemigatinib in the US in patients previously treated with CCA gene fusions or rearrangements and unresectable or metastatic locally advanced FGFR2, representing the first targeted therapy to be approved in this setting. (Rizzo et.al., 2021). However, several questions remain unanswered and further studies will come for further clarification.

Despite the reserved prognosis, imaging diagnosis has advanced, visualizing the exact location of the tumor, whether or not there is an invasion of adjacent structures, which brings security to the medical team bringing security as to resection. New resection techniques have emerged, even if they are palliative.

The case presented had a rapidly progressive and unfavorable evolution. Taking into account the comorbidities, age, late diagnosis and clinical instability of the patient, no surgical techniques were performed. The elucidation of the diagnosis and death occurred in a period of three weeks.

CONCLUSION

Cholangiocarcinoma is a progressively fatal disease that usually occurs due to malignant transformation of hepatic bile cholangiocytes. Its incidence is increasing worldwide and there is an urgency in the diagnosis and effective treatment strategies against this devastating disease.

The identification of biomarkers to aid in the effective diagnosis of cholangiocarcinoma during the early stage of the disease is not satisfactory. Some serum-derived biomarkers, including carcinoembryonic antigen and CA19-9, have shown promise for their application in timely diagnosis, but still suffer from low sensitivity.

We need to advance in research in this area, with the definition of new markers or tests that allow early diagnosis, improving the prognosis of this disease that still remains a challenge in medicine.

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